VOLUME-7, ISSUE-8, AUGUST-2018 • PRINT ISSN No 2277 - 8160

Original Research Paper

General Surgery

EVALUATION OF THE FEASIBILITY OF BREAST CONSERVATION SURGERY AFTER NEO-ADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER

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ABSTRACT 20 patients of histologically proved and locally advanced breast cancer were evaluated for suitability of breast conservation surgery following down staging by neoadjuvant chemotherapy.
All patients were assessed for suitability of breast conservative surgery after 2nd & 4th cycle of chemotherapy, 12 patients (60 %) were found suitable for breast conservation . Thus we conclude that breast conservation surgery is possible in significant number of locally advanced breast cancer, after down staging by neoadjuvant chemotherapy. But histopathological report of the operative specimens shows that 15 patients were potentially suitable for BCS i.e. 75%.

KEYWORDS : Breast Conservation Surgery; Neo-Adjuvant Chemotherapy; Locally Advanced Breast Cancer

INTRODUCTION

Breast cancer is the commonest malignancy of females in the world and second most common cancer of females in India. (1). Though majority of patients present with early breast cancer in western countries due to increased awareness and screening programme, but most of the patient s in our country still present with either locally advanced or metastatic breast cancer. Most of these patients are unsuitable for breast conservation and are treated by mastectomy .

Some of our patients with large tumours express the desire for conservation of the breast, but are denied breast conservation surgery, due to large size of primary tumor. This pilot study was an attempt to evaluate the feasibility of breast conservation following down staging of the tumor using neoadjuvant chemotherapy.
Twenty female patients of histologically proved breast cancer with T3 & T4 lesions, aged below 65 years were included in this study. Staging was done by clinical examination,x-ray chest, skeletal survey, baseline mammogram & ultrasonography of breasts and abdomen.

Response to NACT were assessed clinically, U.S.G. & mammography after 2nd cycle of chemotherapy. In case of good response to NACT, reassessment again done after 4th cycle NACT, for planning of surgery i.e breast conservation surgery or modified radical mastectomy.

MATERIAL AND METHODS

Twenty female patients of histologically proved breast cancer were included in this study. Informed consent was taken from all patients. Patients with large T2 (>4 cm), T3 and T4 lesion s were included in this study. Patients with age >65 years, small tumors (<4 cm) and those with metastatic disease were excluded.

Staging was done by clinical examination, X-ray chest, skeletal survey, a baseline Mammogram and Ultrasonography of breast & abdomen. Routine work up included complete blood picture, liver function tests, renal function tests, ECG and Echocardiography.

Based on preoperative assessment, patients were categorized – a) Those who were suitable for breast conservation surgery (WLE or quadrantectomy + Axillary clearance). b) Those who were are not suitable for breast conservation.

All patients joining the trial were fully informed on the object of trial.

CHEMOTHERAPY REGIMENS: CAF or CMF were used in following schedule:-

Cyclophosphamide 600 mg/m^2 IV day 1, 8
Adriyamycin 30 mg/m^2 IV day 1, 8
OR
Methotrexate 40 mg/m^2 IV day 1, 8
5-fluroraci 600 mg/m^2 IV day 1, 8

- For patients with altered cardiac function, CMF regime was used. Instead of adriamycin, methotrexate was given 40 mg/m^2 IV day 1 and 8.
- All patients were advised to take light food on the day of chemotherapy and injection Ondensetron 8 mg IV was given before chemotherapy.
- A peripheral blood count was performed before each course of chemotherapy and if TLC was found less than 4000/mm^3, chemotherapy was postponed.
- All patients were assessed clinically, mammographically and by USG after 2nd and 4th cycle of chemotherapy, to assess tumor response.

CLINICAL ASSESSMENT OF TUMOR RESPONSE

Maximum diameter of the tumor was measured by calipers – Two greatest perpendicular diameter of the tumor was in the breast was taken and product of both was taken as overall clinical tumor.

RESPONSE WAS CATEGORIZED AS FOLLOWS:

a. ***Complete Response :*** Total disappearance of primary tumor and lymphnodes.
b. ***Partial Response :*** Greater than 50% reduction of the product of two perpendicular diameters.
c. ***Stable Response :*** Reduction of tumor size < 50% or increase in tumor size < 25%.
d. ***Progressive :*** Increase in tumor size in > 25%

MAMMOGRAPHIC ASSESSMENT: Bilateral mammograms were obtained during baseline staging and was repeated after 2nd and 4th cycle of chemotherapy for the affected breast.

Pre and post treatment mammograms were assessed by consultant radiologist.

THE FOLLOWING CRITERIA WAS ASSESSED :

a. ***Mass :*** Size measured on mammogram using a scale in three perpendicular directions (2 maximum dimensions considered). The shape and margins of the lesion and its density compared with the adjacent breast parenchyma.
b. ***Microcalcification :*** Distribution and extent.
c. ***Associated features :*** Architectural distortion, skin thickening, nipple retraction, additional masses and associated lymphadenopathy.

RESPONSE ASSESSMENT BY MAMMOGRAPHY

a. **Complete response:** Complete resolution of mass at

mammography with no residual abnormality

b. **Partial mammographic response:** suggested by the following features.

I. Mass resolved in mammography but microcalcification present.
II. Variable decrease in size and density of mass.
III. Decrease in size of a mass with no change in density.
IV. Size unchanged but density decreased.

c. **Stable disease :** - Findings unchanged from previous mammographic examination.

d. **Progressive disease :** Enlargement of mass or increase in the extent of abnormality.

ULTRASONOGRAPHIC ASSESSMENT

Ultrasonography was done both as a baseline (pre chemotherapy) and after 2nd and 4th cycles of chemotherapy to see the response. Baseline study included assessment of both breasts for tumor size, shape, margins and echo-texture.

RESPONSE ASSESSMENT BY USG:

1. **Complete Response :** Complete disappearance of the mass with no residul abnormality
2. **Partial Response :** Tumor size reduction > 50%.
3. **Stable Response :** Reduction < 50% or increase in size < 25%.
4. **Progressive :** Tumor size increasing > 25%.

In addition bilateral axilla and the liver was also evaluated on ultrasound for any abnormality and for staging.

Following completion of 4 cycles of chemotherapy patients were reassessed clinically, mammographically and by Ultrasonogram and suitability for breast conservation was assessed.

The actual surgical procedure performed was then recorded. A detailed histopathalogical evaluation was done and a formal pathological TNM (pTNM) staging was recorded.

Postoperatively completion chemotherapy and/or radio therapy was given where indicated. Patients were followed up regularly in breast cancer clinic and any evidence of loco-regional or distant metastasis was recorded.

Result

Table showing Distribution of patients according to Age. Tumour size, Lymph node status		
Age Grps(yrs)	No.	%
20-30	2	10
31-40	5	25
41-50	9	45
51-60	4	20
Tumor size (cm)		
5-6	11	55
6-7	3	15
7-8	2	10
8-9	4	20

20 female patients with breast cancer were included in this study.

The demographic data of the patient is as follows:

Age: Mean age of the patient was 44.65 years with a range of 29-60 years. Age distribution and percentage of patients undergoing study is shown in table 1 as follows:

Table 1:

Age Group (years)	No. of patients	Percentage
20-30	2	(10%)
31-40	5	(25%)
41-50	9	(45%)
51-60	4	(20%)

Menopausal Status

10 Patients were premenopausal and 2 patients were perimenopausal and 8 patients were post menopausal of which 2 patients had undergone hysterectomy.

Tumor size (T Status) - Tumor size of the patients is shown in table 2 as follows:

Table 2:

Tumor	No. of patients	Percentage
T2 (4-5 cm)	5	(25%)
T3	7	(35%)
T4a	8	(40%)

Details of tumor size are shown in table 3 as follows:

Table 3:

Tumor size in cm	No. of patients	Percentage
4-5	5	(25%)
5-6	6	(30%)
6-7	3	(15%)
7-8	2	(10%)
8-9	4	(20%)

Distribution of patients according to lymph node status is shown in Table 4 as follows:

Table 4:

Lymph node (N)	No. of patients	Percentage
Node negative	9	(425%)
Node positive	11	(55%)
Total	20	(100%)

Distribution according to Clinical staging (TNM) is shown in the Table 5 as follows:

Table 5:

Tumor	No. of patients	Percentage
IIA	4	(20%)
IIB	4	(30%)
IIIA	4	(10%)
IIIB	8	(40%)

Neoadjuvant Chemotherpy: 19 patients received CAF and one patient received CMF regimen. All patients received preoperative chemotherapy. 14 patients completed all 6 cycles. 5 patients took only one cycle of postoperative

Chemotherapy Tolerance: 19 patients tolerated the chemotherapy well, except minor toxicities. One patient developed severe low TLC, sore throat, nausea, vomiting etc for which she was hospitalized and treated. Toxicity due to chemotherapy is given in table 6.

Overall toxicity distribution and most common toxicities are shown in Table 6 as follows:

Table 6:

Overall toxicity	Post Op (n = 20)		Pre Op (n = 20)	
	No. of Patients	Percentage	No. of Patients	Percentage
None	9	45	9	45
Grade I	10	50	10	50
Grade II	0	0	0	0
Grade III	0	0	0	0
Grade IV	1	5	1	5
WBC Count				
Grade I (3.0-3.9)X103	6	30	2	10
Grade II (2.0-2.9)X103	2	10	1	5
Grade III (1.0-1.9)X103	1	5	1	5
Grade IV (<1.0)X103	1	5	0	0

INFECTION	0	0	0	0
Severe	0	0	0	0
Life threatening	0	0	0	0
Death				
SEPTIC EPICODE	0	0	0	0
NAUSEA				20
Decreased dietary intake (Grade 2)	6	30	4	0
No dietary intake (Grade 3)	0	0	0	
VOMITING				
6-10 episodes/d	1	5	0	0
Parenteral support required	0	0	0	0
DIARRHOEA				
7-9 times stool/day	1	5	0	0
10+ times /d, bloody stool or parenteral support required	0	0	0	0
STOMATITS				
Unable to eat	6	30	4	20
Parental support required	0	0	0	0
ALOPACIA				
Mild	2	10	2	10
Pronounced	3	15	3	15
Complete	15	75	15	75
PHLEBILITIS/ THROMBOEMBOLISM				
Supf.	3	15	4	20

Post Chemotherapy Evaluation

Clinical Response: The overall response rate of the primary tumor to the neoadjuvant chemotherapy was 95% (complete response 45%, partial response 50%). One patient had progression of disease and was offered surgery after two cycles. However, for some personal reasons she delayed the surgery and got operated only after four cycles.

Distribution of patients according to clinical response is shown in table 7 as follows:

Table 7:

Response	No. of Patients	Percentage
Complete response (CR)	9	45%
Partial response (PR)	10	50%
No response (NR)	0	0%
Progressive	1	5%
Total	20	100%

Post Chemotherapy down-staging shown in the table 8 as follows:

Stage	No. of patients	(%)
	Pre Chemotherapy	Post Chemotherapy
No tumor (Clinically)		9 (45%)
I		5 (25%)
IIA	4 (20%)	4 (20%)
IIB	4 (20%)	2 (10%)
IIIA	4 (20%)	0 (00%)
IIIB	8 (40%)	0 (00%)

Mammographic Response: 18 patients underwent Mammographic examination before neoadjuvant, while 19 patients had mammogram done following chemotherapy. In one patient mammogram did not show any measurable lesion and thus pre and post chemotherapy mammogram could be compared in 17 patients. Overall mammographic response rate was 82.2%. Responses were complete in 2 (11.7%) patients and partial in 12 (70.5%) patients. No response / or progressive in 3 (17.6%) patients.

Distribution of patients according to mammographic response is shown in table 9 as follows:

Table 9:

Response	No. of Patients	Percentage
Complete response (CR)	5	25%
Partial response (PR)	12	60%
No response (NR) / Progressive	3	15%
Total	20	100%

Ultrasonographic response: 17 patients underwent ultrasonographic examination of the breast before starting neoadjuvant chemotherapy while 19 patients underwent Ultrasonography, post CT. The overall objective response of primary tumor to neoadjuvant chemotherapy was above 88.1% (complete 5.8% and partial 82.3%).

Distribution of patients according to ultrasonographic response is shown in table 10 as follows:

Table 10:

Response	No. of Patients	Percentage
Complete response (CR)	1	5.8%
Partial response (PR)	14	82.3%
No response (NR) / Progressive	1	11.7%
Total	16	100%

Assessment of suitability of breast conservation and plan of surgery: 12 patients (60%) were found suitable for breast conservation. Of these 3 patients opted for modified radical mastectomy while 9 opted for breast conservation.

Surgical procedure done: Following neoadjuvant chemotheraphy surgery was performed in all patients. Four patients underwent quadratectomy + axillary clearance while five patients underwent WLE + axillary clearance. One patient had to undergo completion mastectomy, because of positive margins on histopathological examination. Finally total 8 patients (40%) underwent conservative surgery.

All eight patients found suitable for breast conservation underwent modified radical mastectomy.

The unsuitability for breast conservation in these patients was based on following criteria:

1. No response / progression based on combined clinical and radiological assessment.
2. Diffuse residual microcalcification.
3. Tumor site and size unsuitable for conservative surgery.

Histopathological Evaluation: Complete histopathological response seen in five patients (25%) in whom there was no evidence of any microscopic disease in the resected breast or lymph nodes. All other 15 patients had evidence of invasive microscopic disease in the specimen. Histopathological evaluation of those 11 patients who underwent MRM revealed that 6 patients in this group were potentially suitable for breast conservation due to either absence of any microscopic disease or presence of very small residual disease. Rest 5 were unsuitable for breast conservation. The findings are summarized as below:

Histopathological evaluation of surgical specimen
- Pathological CR 5 (25%)
- Histopathological evaluation of mastectomy (11)
- Potentially suitable for breast conservation 6 (53%)
- Unsuitable for breast conservation 5 (45%)

Post 4th Cycle Chemotherapy Evaluation: 12 patients were found suitable for breast conservation. Of these, 3 patients opted for MRM. 9 patients opted for BCS.

Post operative Histopathological report showed 15 patients were potentially suitable for BCS (75%).

Surgical procedure done in BCS was – wide local exicision with

axillary clearance. Of these nine patient, one patient had to undergo completion mastectomy for positive margin in pathological specimen.

Follow up period: 15-16 years

One patient died 10 months after MRM to local and systemic recurrence.

One patient following MRM died at 8 years due to systematic recurrence. One patient died at 15 years due to systemic recurrence following MRM. Of these 8 patients, who had undergone BCS finally, one patient of stage IIIB had local recurrence at two years and were subsequently treated by MRM and irradiation to chest wall, died at 5 years due to systemic recurrence. Total of 4 patients died due to local and systemic recurrence within 15 years, under this study is 4 of which had IIIB Breast Cancer at the beginning of this study, only one patient had undergone BCS for stage IIIA Breast Cancer and remaining had undergone MRM. No. of BCS undergone in stage IIIB is nil.

Five years relative survival rate for women with breast cancer, stage III – 85%, in our study.

10 years survival in our study is 80% (4 out of 20)

5 years survival in case of breast cancer carcinoma regional lymph node positively is 73% in our study (3 patients died out of 11 lymph node positive patient.

Survival at 19 years (greater than 15 years) is 75% (5 patients died out of 20)

DISCUSSION

Neoadjuvant chemotherapy is being used increasingly in the treatment of patients with large operable and locally advanced breast cancer with the aim of reducing the size of the primary tumor and eliminating micro metastasis, in order to improve prognosis (2, 4, 5). Though the extent of surgery following neoadjuvant chemotherapy is not clearly defined, the high response rates with neoadjuvant chemotherapy have stimulated interest in the use of conservative surgery for patient with large operable and LABC (2, 3, 4, 5).

A wide variety of regimens have been used as neoadjuvant chemotherapy. Most regimens incorporate doxorubicin (Adriamycin). These regimens produce a complete pathological remission ranging from 3-18%. We used CAF in 19 patients while one patient received CMF. There are no randomized trials comparing CAF with CMF in the setting of neoadjuvant chemotherapy. Two trials have suggested that response rates are lower with CMF (6, 7). In a previous trial reported from AIIMS NEW DELHI, significantly better response rates were seen with CAF regiment as compared to CMF (7). There is no apparent trend towards better response among various doxorubicin containing regimens (4).

Nineteen of our patients (95%) showed some degree of tumor reduction. Nine patients (45%) had complete clinical response, while 10 patients showed partial response (50%). Only one patient had progression of disease on clinical examination. These response rates are similar to those reported in literature using different regimens (8, 9).

Singletary et al (8) used three cycles of vincristine, doxorubicin, cyclophosphamide and prednisone (VACP) at 21 day intervals and found 16% complete clinical response and 84% partial clinical response of which 23% became potential candidates for breast conservation surgery. Scholl et al (9) used 4 cyles of CAF as neoadjuvant chemotherapy and achieved objective rates of 65%.

A complete clinical response rate 66% and overall response rate 98% was reported by Smith et al (10), using chemotherapy regimen requiring continuous infusion of drugs for 6 months. In our study, the regimen used, resulted in excellent patient compliance and low incidence of minor toxicities, like vomiting, anorexia, superficial thromobophelbitis etc. Only one patient develop severe neutropenia for which she was hospitalized and treated. She subsequently received scheduled preoperative chemotherapy. All other patients completed scheduled chemotherapy.

Clinical response rates are believed to be important because this may correlate with patient survival (9) and also help in deciding the further surgical treatment. However it is found that response to chemotherapy is over estimated with clinical examination (11,12). As many as one third of patients thought to be in complete remission on clinical grounds, may have residual disease on pathological examination (13, 14). On the other hand persistence of residual abnormalities on physical examination or mammograpgy does not always mean persistence of pathological disease (13).

In our study 9 patient had clinical CR but only 5 patient had pathological CR, 3 out of 9 patients who had clinical CR, pathologically they had complete response. On the other hand, 2 patients, those who had partial response clinically, were found in complete remission pathologically.Therefore, in adition to clinical examination, patients in our study were also assessed by mammography and ultrasonography at the end of 2nd and 4th cycle chemotherapy.

Mark C. Segal et al reported excellent and moderate mammographic response in 82% cases. Cocconi's et al (6) reported a complete response rate of 8% with clinical examination, of 0% with mammography and of 14 % with pathologic examination. Assessment of response to therapy by imaging modalities is important because this is crucial in choosing optimal surgical therapy and also because clinical examination often overestimates in tumor size (15, 16).

In our study, the response to neoadjuvant chemotherapy was assessed by mammography in 17 cases and by ultrasonography in 16 cases. Mammography response was seen in 82% cases (15). Cocconi et al (6) reported a complete response rate of 8% with clinical examination, 0% with mammography. In one patient with clinically palpable lesion, mammogram did not show lesion due to the presence of dense glandular parenchyma.

Breast conservation following neoadjuvant chemotherapy in large operable and LABC has been attempted by various authors. Singletary et al (8) retrospectively analyzed patients undergoing mastectomy following neoadjuvant chemotherapy and reported that 23% of patients was potential candidates for breast conservation. Others in prospective studies, have reported for breast conservation rates of 31-44% (4, 14, 17) following down staging with neoadjuvant chemotherapy. Twelve patients (60%) were considered suitable for breast conservation in our study after neoadjuvant chemotherapy. However only 8 patients (40%) enventually underwbt breast conservation as 3 patients preferred mastectomy and one patient had to undergo mastectomy due to positive margins on histopathology, following BCS.

Breast conservation achieved in our study is thus comparable to that reported in literature (4, 14, 15, 17). Histopathological evaluation of mastectomy as primary surgical procedure were potentially suitable for breast conservation. It is patient to mention that only one patient out of 8 with T4a lesion underwent breast conservation as compared to 7 out of 12 with T3 lesions. Thus it appears that T4a lesion are less likely to undergo breast conservation as compared to T3 lesion. Complete pathological response rates 3-44% have been reported by various authors (4, 5) following neoadjuvant chemotherapy. Five (25%) of our patients had complete pathological response. A sub group analysis revealed that similar percentage of patients with T3 lesions and T4a lesions had shown complete pathological response. Two out of 8 (25%) patients with T4a lesions had shown p-CR while 3 out of 12 (25%) patients with T3 lesions had shown p-CR. When we compared clinical CR to clinical nodal status at presentation, it was found that four out of 11

lymphnode positive patients (37%) had clinical CR as compared to 5 out of 9 node negative patients (55%). This is consistent with findings of Fisher et al (5) who found that C-CR rates were nearly similar in patients with ≥5 cm tumors regardless of their nodal status at presentation. In contrast only 1 out of 9 clinically node negative patient (11%) showed pathological CR as compare to 4 out of 11 node positive patients (37%). This is also consistent with findings of Fisher et al (5) who found pCR to be higher in women with clinically positive nodes as compared to women with clinically negative nodes (30% vs 24%).Various studies have reported a satisfactory loco-regional control with a local relapse rate of 1-19% (4, 14, 17) following breast conservation after induction chemotherapy. Similarly satisfactory 3-5 years survival ranging from 73-77% has also been reported in these patients (14, 17). Follow up duration in our patients is too short to make any meaningful conclusions regarding the survival. Only one patient died at 10 months due to loco-regional and distant failure. This patient had undergone MRM. No other patients have had any loco-regional or distant relapse.

SUMMARY & CONCLUSIONS

20 patients of histologically proven large operable and locally advanced breast cancer were evaluated for suitability of breast conservation surgery following down staging by neoadjuvant chemotherapy. All patients were assessed clinically, Mamographically, and by ultrasonography before starting chemotherapy, after second cycle of chemotherapy and finally before operation. Response to chemotherapy was assesses by clinical examination, ultrasonograpgy and mammography. Conservative surgery is possible in a significant number of locally advanced breast cancer, after down staging by neoadjuvant chemotherapy.

REFERENCE

1. Park JE, Preventive and Social medicine.
2. Jacquillat C, Weil M, Auclerc G et el. Neoadjuvant chemotherapy in the conservative management of breast cancer: Study on 205 patients in Jacquillat, Weil M, Khyat D eds. Neo-adjuvant chemotherapy. Paris , Colloque INSER M: John Libbey Eurotext Ltd. 1986; 137: 197-206.
3. Hortobagyi GN, Ames FC, Buzdar AU et al. Management of stage III primary breast cancer with primary chemotherapy, surgery and radiation therapy. Cancer 1988: 62: 2507-2516.
4. Amin E, Steven Dh, Andrew Wh et al. Teatment of large and locally advanced breast cancers using neoadjuvant chemotherapy. The American Journal of Surg 1998; 175: 127-132.
5. Fisher B, Brown A, Mamonous E, Wieand S et al. Effect of preoperative chemotherapy on local regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncolte 1997: 15 (7): 2483-2493
6. Cocconi G, Di Blassic B, Bisagni G et al. Neoadjuvant chemotherapy or chemotherapy and endrocine therapy in locally advanced breast carcinoma: A prospective randomized study. Am J Clin Oncol 1990; 13: 226-232.
7. Gupta P, Bijlani L, Rath GH et al. Neoadjuvant chemotherapy with cyclophosphamide, doxorubicin and 5FU (CAF) or cyclophosphamide, methotrex and 5-FU (CMF) in 69 cases of locally advanced (stage IIb) breast cance. Jpn J Surg 1991; 21: 637-642.
8. Singletary Se, McNeese MD, Hotobagyi GN, Feasibility of breast conservation surgery after induction chemotherapy for locally advanced brest cancer. Cancer 1992; 69: 2849-2852.
9. Scholl SM, Piegra JY, Assclain B et al. Breast tumor response to primary chemotherapy predicts local and distal control as wel as survival. Eur J Cancer 1995; 31A(12): 1969-1975.
10. Smith IE, Jones Al, O'Brien MER, Nickinna JA, Sacks N, Baun M, Neoadjuvant chemotherapy for operable beast cancer. Eur J Cancer 1993; 29: 592-595.
11. Cocconi G, Di Blasio B, Albert G, Bisagni G, Botti E, Peracchia G. Problems in evaluating response of primary breast cancer to systemic therapy. Beast Cance Res Treat 1984; 4: 309-313.
12. Dickson RB, Lippman MG, Cancer of the breast. In: Devita Jr. VT. Hellman S, Roghburg SA (editos). Lippincott – aven Philadelphia 1997; pp. 1541-1616.
13. Vinnicombe SJ, MacVicar AD, Guy RL et al. Primary breast cancer: Mammographic changes after neoadjuvant chemotherapy, with pathological correlation. Radioi 1996; 198: 333-340.
14. Clark J, Rosenman J, Cance W, Haele J, Graham M. Extending the indication for breast conserving reatment t patients with locally advanced breast cancer. Int J Radiat Oncol Biol Phys 1998; 42: 345-350.
15. Segel MC, Paulus DD, Hortobagyi GN. Advanced primary breast cancer: assessment at mammography of response to induction chemotherapy, Radiology 1988; 169: 49-54.
16. Fomage BD, Toubas O, Morel M. Mamgraphic and sonographic determination of pre-operative breast cancer. Cance 1987; 60: 765-771.
17. Schwartz GF, Bichansky CA, Kamamicky LT et al. Induction chemotherapy follow by breast conservation for locally advanced carcinoma of the breast. Cancer 1994; 73: 362-369.